**Appendix C- Articles**

**(#1) DNA Mismatch Repair Happens Only During a Brief Window of Opportunity**

*ScienceDaily (Dec. 22, 2011)* — In eukaryotes -- the group of organisms that include humans -- a key to survival is the ability of certain proteins to quickly and accurately repair genetic errors that occur when DNA is replicated to make new cells.

In a paper published in the December 23, 2011 issue of the journal *Science,* researchers at the Ludwig Institute for Cancer Research and the University of California, San Diego School of Medicine have solved part of the mystery of how these proteins do their job, a process called DNA mismatch repair (MMR).

"One of the major questions in MMR is how MMR proteins figure out which base in a DNA mispair is the wrong one," said Ludwig Institute assistant investigator Christopher D. Putnam, PhD, an adjunct assistant professor of medicine at UC San Diego. "For example, if guanine (G) is inappropriately in a base-pair with thymine (T), is the G or the T the error? Picking the wrong base results in mutations, not fixes."

Using *Saccharomyces cerevisiae, or baker's yeast,*as their model organism, the researchers, led by Richard D. Kolodner, PhD, Ludwig Institute investigator and UCSD professor of medicine and cellular and molecular medicine, discovered that newly replicated DNA produces a temporary signal for 10 to 15 minutes after replication which helps identify it as new -- and thus a potential subject for MMR.

The actual signal was not identified, but Putnam said it might be tell-tale nicks in single-stranded DNA or certain proteins associated with replication. The scientists are working to pinpoint the precise signal.

The findings, combined with earlier, published work that visualized MMR in a living cell for the first time, more fully explains how eukaryotes eliminate DNA replication errors, which can result in defects and the development of cancers.

"How eukaryotes identify the newly synthesized strand of DNA is a mystery that has persisted for at least 30 years," said Putnam. "These findings really change our ideas of how MMR works," said Putnam.

Co-authors include Hans Hombauer and Anjana Srivatsan of the Ludwig Institute for Cancer Research, UCSD Departments of Medicine and Cellular and Molecular Medicine, Institute of Genomic Medicine and UC San Diego Moores Cancer Center.

Funding for this research came from the National Institutes of Health.

# (#2) Frogs Use Calls to Find Mates With Matching Chromosomes; Tree Frogs That Look Similar Hear Chromosome Difference in Calls

*ScienceDaily (Dec. 27, 2011)* — When it comes to love songs, female tree frogs are pretty picky. According to a new study from the University of Missouri, certain female tree frogs may be remarkably attuned to the songs of mates who share the same number of chromosomes as they do. The discovery offers insight into how new frog species may have evolved.

Carl Gerhardt, Curators Professor of Biological Sciences in the MU College of Arts and Science and doctoral student Mitch Tucker studied two closely related species of grey tree frogs that live in Missouri, the eastern grey tree frog (*Hyla versicolor*) and the Cope's grey tree frog (*H. chrysoscelis*).

"To the naked eye -- human and frog -- the two frogs look exactly alike," Gerhardt said. "The frogs differ only in the number of chromosomes. The eastern grey tree frog has double the number of chromosomes."

To the ears of potential mates, the two species differ in their vocal performances.

"The males are both singing the same love song -- just one frog is singing it slower. It's kind of like the difference between Eric Clapton's original and unplugged versions of *Layla,"* Tucker said.

In previous studies, the scientists found that tree frogs with more sets of chromosome have larger cell sizes, which slows down the trill rate. What was not known was whether the calling preferences of females are similarly linked to chromosome number.

To answer this question, Tucker simulated the chromosome duplication event by replicating spring temperatures early in the frog development. Females were grown to maturity and then exposed to computer-generated, synthetic male calls that differed by trill rate. They found that the females hopped toward the calls with the trill rate of the males with matching chromosome numbers, which indicates female preference.

"This shows that chromosome number alone can control the behavior that keeps the species separate," Gerhardt said. "In turn, as chromosome number increases, so does the size of cells, which is probably the immediate cause of the changes in calls and preferences."

In animals, the origin of species is often associated with geographic barriers. A large body of water or range of mountains, for example, splits a large population and prevents mating. The eastern grey tree frog, according to Gerhardt, may represent a rare case of rapid evolution occurring by chromosome duplication, changes in behavior and reproductive isolation.

The report, titled "Parallel changes in mate-attracting calls and female preferences in autotriploid tree frogs," was published by the journal *Proceedings of the Royal Society B-Biological Sciences*. The study was supported by funding from the National Science Foundation, National Institutes of Health, and the University of Missouri Research Board.

**(#3) Major breast cancer breakthrough announced at BC Cancer Agency**

VANCOUVER, Oct. 7, 2009  /PRNewswire/ - For the first time in history, BC Cancer Agency scientists in British Columbia, Canadahave decoded all of the three billion letters in the DNA sequence of a metastatic lobular breast cancer tumour, a type of breast cancer which accounts for about 10 per cent of all breast cancers, and have found all of the mutations, or "spelling" mistakes that caused the cancer to spread.

The landmark study, which will be published October 8th as the cover story in the prestigious international science journal Nature, helps unlock the secrets of how cancer begins and spreads, thus pointing the way to the development of new breast cancer treatment targets and therapies.

"One in nine women is expected to develop breast cancer, and breast cancer accounts for 29 per cent of all cancer diagnoses for B.C. women," said Health Services Minister Kevin Falcon. "As a result of the efforts of the scientists behind the study, this breakthrough finding gives further hope to the thousands of women with this terrible disease."

"I never thought I would see this in my lifetime," said Dr. Samuel Aparicio, head of the breast cancer research program at the BC Cancer Agency, an agency of the Provincial Health Services Authority (PHSA). "This is a watershed event in our ability to understand the causes of breast cancer and to develop personalized medicines for our patients. The number of doors that can now be opened to future research is considerable."

Partnering with the BC Cancer Agency's Genome Sciences Centre, Dr. Aparicio's team used the latest in next-generation DNA sequencing technology to study the evolution of a single patient's lobular breast cancer tumour over a nine-year interval. They found 32 mutations in the metastatic cancer tumour and then looked to see how many of those same spelling mistakes were present in the original tumour. The result was surprising - only five of the 32 could have been present in all of the cells of the primary tumour, thus fingering them as the criminals that caused the disease to get started in the first place. These five mutations were previously unknown to researchers as playing a role in cancer.

"This study demonstrates the remarkable capacity of next-generation DNA sequencing technology," says Dr. Marco Marra, Director, BC Cancer Agency's Genome Sciences Centre. "The project that decoded the first human genome in 2001 took years and an enormous amount of funding. We were able to sequence the breast cancer genome in weeks and at a fraction of the cost."

"Through our research at the BC Cancer Agency, we are dedicated to finding new and novel ways to detect cancer earlier and to develop more enhanced treatments," said Brian Schmidt, Interim President, BC Cancer Agency and Senior Vice President, Provincial Services, Population and Public Health, PHSA. "This discovery is a wonderful example of how investment in research is helping to pave the way toward better outcomes for cancer patients in the future."

The discovery is not only a major scientific milestone for the BC Cancer Agency, an acknowledged world leader in cancer research care, but also a significant testimony to the power of philanthropy invested in science to fuel cancer research and drive new discoveries.

"The BC Cancer Foundation, as the fundraising arm of the agency, has raised over $15 million to support breast cancer research at the BC Cancer Agency across the province, including Dr. Aparicio's program, through its Weekend to End Breast Cancer walk," said BC Cancer Foundation President and CEO Douglas Nelson. "We are very grateful to the many thousands of British Columbians who have walked, donated and supported The Weekend to End Breast Cancer over the past six years. To everyone who has walked or contributed we can confidently say your efforts have made a difference - you are a partner in this remarkable achievement."

The BC Cancer Foundation founded the BC Cancer Agency's Genome Sciences Centre, the Centre for Translational and Applied Genomics at the BC Cancer Agency, and the BC Cancer Agency's Breast Cancer Outcomes Unit, all of which played a key role in the study. The research was conducted in the BC Cancer Agency's research centre in Vancouver, which was constructed by the BC Cancer Foundation, with donor and provincial and federal government funding.

The Canadian Breast Cancer Foundation, BC/Yukon Region supported a key member of Dr. Aparicio's research team through a bioinformatics fellowship. Other funders and supporters include the Canadian Institutes for Health Research, Genome Canada and Genome BC, the Canadian Foundation for Innovation, and the Michael Smith Foundation for Health Research.

Dr. Aparicio was recruited in 2005 from Cambridge University, UK to develop a breast cancer research program in British Columbia at the BC Cancer Agency. He holds the Nan and Lorraine Robertson Chair in Breast Cancer Research at theUniversity of British Columbia (UBC), the Canada Research Chair in Molecular Oncology and is a professor in the Department of Pathology and Laboratory Medicine at UBC.

The BC Cancer Agency is committed to reducing the incidence of cancer, reducing the mortality from cancer and improving the quality of life of those living with cancer. It provides a comprehensive cancer control program by working with community partners to deliver a range of oncology services, including prevention, early detection, diagnosis and treatment, research, education, supportive care, rehabilitation and palliative care. The BC Cancer Foundation raises funds to support research and enhancements to patient care at the BC Cancer Agency throughout B.C.

# (#4) Cold Cases Gone Hot: Researchers Solve Decades-Old Medical Mysteries Using Genetics

*ScienceDaily (Jan. 28, 2011)* — The mystery began in 1976. Adolfo Pampena was diagnosed with a rare form of cancer that caused a strange combination of symptoms and was associated with the occurrence of multiple tumours in his stomach and colon. His medical team was stumped and was unable to answer the most important questions for him and his family: the cause of his disease and the risk for future generations.

Now, 35 years later, the answers are at hand thanks to a genetic study led by investigators at the Research Institute of the McGill University Health Centre (RI MUHC), the McGill Program in Cancer Genetics at the Gerald Bronfman Centre for Clinical Research in Oncology and the Lady Davis Institute for Medical Research at the Jewish General Hospital. The study was recently published in *The New England Journal of Medicine (NEJM).*

The researchers were able to pinpoint the gene responsible for the disease (*BUB1B*), which is involved in the regulation of chromosomal separation. Instability during cell division can result in chromosomes ending up in the wrong place, which can lead to the development of tumours. "The general significance of this discovery is that individuals can be seen at our genetic clinic with an unknown condition and end up with a diagnosis that is relevant to patients and their families," said Dr. William Foulkes, senior author of the study and a researcher in genetics at the RI MUHC, the Lady Davis Institute.

"My father and family were relieved that the cancer risk for other family members is much less than we thought," said Mary Pampena, Adolfo's daughter. "Now we know more about my father's genetic history and the cancers he had. We know what screening test to do in the future. This is important information for us, our children and future generations."

In another study published in the January, 2011 *Journal of the American Medical Association (JAMA).* Dr. Foulkes details a second solved mystery involving five families with a long history of nontoxic multinodular goiter (MNG). Goiter is a thyroid disease which can lead to extreme swelling of the neck or larynx. The most common form of the disease is not genetic and is due to iodine insufficiency. However, this form of MNG was known to be genetic, but to date, no one had ever localized the specific gene or mutation responsible. Dr. Foulkes, Dr. Marc Tischkowitz (from the Program in Cancer Genetics and the Lady Davis Institute) and their team finally succeeded, and found the mutation in a surprising place.

As it turns out, the mutation, in a gene called *DICER1*, was extremely unusual, Foulkes said, who is also James McGill Professor of Medicine, Human Genetics and Oncology and Director of the Program in Cancer Genetics at McGill University. "It changes the protein in only one place, and that single change is enough to trigger multinodular goiter. Generally speaking, when you have a mutation in a disease gene, it causes a multitude of problems, not just one illness. But in this case, we have no evidence that it causes anything except goiter.

Intriguingly, women in three of the families had been diagnosed with an unusual type of ovarian tumor called Sertoli-Leydig Cell Tumor and thus Foulkes and his colleagues were able confirm that there is a genetic link between multi-nodular goiter and these rare tumors. This link had first been postulated in 1974.

"In the future, our challenge as researchers is to be able to help people with an unknown condition by finding out rather quickly what the genetic cause of their problem is" explained Foulkes. "We can hope in the long-term to have an impact on treatment, diagnosis and other aspect of management."

# (#5) Coffee Drinking in Your Genes? Genetic Variants in Two Genes Linked With Caffeine Intake

*ScienceDaily (Apr. 6, 2011)* — Two genes in which variation affects intake of caffeine, the most widely consumed stimulant in the world, have been discovered. A team of investigators from the National Cancer Institute, Harvard School of Public Health, Brigham and Women's Hospital, and the University of North Carolina at Chapel Hill examined genetic variation across the entire genome of more than 47,000 individuals from the U.S., as described in the open-access journal *PLoS Genetics*.

The genes identified were CYP1A2, which has previously been implicated in the metabolism of caffeine, and AHR, involved in the regulation of CYP1A2. Individuals with the highest-consumption genotype for either gene consumed ~40 mg more caffeine than those with the lowest-consumption genotype, equivalent to the amount of 1/3 cup of caffeinated coffee, or 1 can of cola.

Caffeine is implicated in numerous physiological and medical conditions; it affects sleep patterns, energy levels, mood, and mental and physical performance. The identification of genes that have an impact on daily consumption offers opportunities to better understand these conditions. Further exploration of the identified genetic variants may provide insight into the speed of caffeine metabolism, how long caffeine circulates in the blood, or how strong the physiological effects of consuming a given amount of caffeine are.

Apart from smoking, genetic determinants of lifestyle behaviors have generally not been consistently described. This study is among the first to examine the entire genome for a relationship between genetics and caffeine intake, a lifestyle behavior relevant to over 90% of U.S. adults. The study's success also suggests that additional genetic determinants of dietary and lifestyle behaviors may be identified in the future using a similar genome-based research strategy.